The Comparative Analysis of Biochemical Parameters in Patients with Pleural Effusions: A Prospective Study

Plevral Effüzyonlu Hastalarda Biyokimyasal Parametrelerin Karsılastırmalı Analizi: Prospektif Bir Çalışma

Analysis of Biochemical Parameters in Pleural Effusions

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Özet

Amaç: Plevra sıvılarında transuda eksuda ayırımı, sıvının etyolojisi ile ilgili hangi ileri tetkiklerin yapılmasının gerekliliği ve tedavi stratejilerinin belirlenmesi hakkında fikir vermesi nedeniyle önemlidir. Amacımız plevra sıvılarında transuda eksuda ayırımı için light kriterleri ile birlikte diğer biyokimyasal parametrelerin tanı değerini araştırmaktır. Gereç ve Yöntem: Etyolojisi bilinmeyen plevral effüzyonlu 52 olgunun LDH, total protein, Albumin, ADA, Apolipoprotein A1, Apolipoprotein B, Lipoprotein-a, Kolesterol, HDL-kolesterol, VLDL-kolesterol, LDL-kolesterol ve Trigliserit parametreleri hem plevral sıvı hasta serumlarında eşzamanlı ölçüldü. Gruplar arası karşılaştırmalarda Mann-Whitney U testi kullanıldı, buna göre $p < 0,05$ ise anlamlı kabul edildi. Eksüda ve transüda ayrımında her bir biyokimyasal parametrenin duyarlılığı, özgüllük ve etkinliği hesaplandı. Verilerin istatistiksel analizinde her bir test için en iyi kesim değeri ROC eğrisi kullanılarak ortaya çıkartıldı, optimum cut-off seviyesi en yüksek toplam duyarlılık ve özgüllük değeri oluşan noktadan seçildi Bulgular: Transüda-eksüda ayrımında plevral LDH (p=0,001), Total protein (p=0,001), Albumin (p=0,001), Trigliserit (p=0,001), Kolesterol (p=0,001), HDL-kolesterol (p=0,042), VLDL-kolesterol (p=0,001), LDL-kolesterol (p=0,001), Apolipoprotein A1 (p=0,021) ve HDL-kolesterol/LDL kolesterol oranı (p=0,048) anlamlı olarak tespit edildi. Tartışma: Sonuç olarak bu çalışmada, plevral LDH, kolesterol ve HDL-kolesterol'ün birlikte kullanılması, Light kriterlerindeki değerlerin kullanılmasına göre istatistiki olarak daha anlamlı bulunmuştur. Bu oranlar %99 duyarlılık, %94,1 özgüllük ve %96,2 doğruluk oranlarına sahiptir.

Anahtar Kelimeler

Plevral Sıvı; HDL; Malign Plevral Effüzyonlar

Abstract

Aim: The differentiation of exudative from transudative effusion is important to lead the clinician in making further biochemical analysis for possible etiology and in choosing the appropriate treatment strategy. The aim of the study is to evaluate the diagnostic value of biochemical parameters together with Light's criteria to differentiate exudative from transudative effusions. Material and Method: The LDH, total protein, albumin, adenosine deaminase (ADA), apolipoprotein A1, apolipoprotein B, Lipoprotein-A, total cholesterol, HDL-cholesterol, VLDL-cholesterol, LDL-cholesterol, and triglyceride levels of patients with unknown etiology were measured both in plasma and pleural fluid. Mann-Whitney U was used to compare the groups and $p < 0.05$ was accepted as statistical significance. Sensitivity, specificity, and accuracy were calculated for each biochemical parameter. The ROC analysis was used to estimate the optimum cut-off value for the highest sensitivity and specificity. Results: Pleural LDH (p=0.001), total protein (p=0.001), albumin (p=0.001), triglyceride (p=0.001), total cholesterol (p=0.001), HDL-cholesterol (p=0.042), VLDL-cholesterol (p=0.001), LDL-cholesterol (p=0.001), apolipoprotein A1 (p=0.021), and HDL-cholesterol/LDL-cholesterol ratio (p=0.048) were found significant in differentiating exudative from transudative effusions. Discussion: The study showed that the use of pleural LDH, total cholesterol, and HDL-cholesterol levels together is more significant than Light's criteria. The sensitivity, specificity, and accuracy of this test were 99%, 94.1%, and 96.2% respectively.

Keywords

Pleural Effusion; HDL Cholesterol; Malignant Pleural Effusion

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Introduction

Pleural effusion, described as collection of fluid in the pleural space, is a very frequent clinical situation for both chest physicians and surgeons. The crucial issue is to determine the etiology of the effusion. It is important to start with the least invasive and the most cost-effective method. Light's criteria have been used to differentiate exudative from transudative effusions. Despite the long use of these criteria, from 1972 to the present time, researchers continue to look for more valuable and easier methods [1].

In this study we prospectively investigated the value of adenosine deaminase (ADA), apolipoprotein A1, apolipoprotein B, Lipoprotein-A, total cholesterol, HDL-cholesterol, VLDL-cholesterol, LDL-cholesterol, and triglyceride levels in plasma and pleural fluid to differentiate the exudative from transudative fluids in patients with pleural effusion without a definite etiology.

Material and Method

The study included 63 patients with pleural effusion without a definite etiology. Eleven of these were excluded from the study due to ambiguous etiology. Total protein, albumin, LDH, ADA, total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1, apolipoprotein B, and lipoprotein levels were measured simultaneously both in plasma and in pleural fluid that was taken by thoracentesis in all cases.

The classification of pleural fluid into transudates and exudates was based on the etiological diagnosis. The diagnosis of the diseases was made by history, physical examination, appropriate biochemical analysis of the serum and pleural fluid of the patients, and cyto-histo-pathologic examination. In cases where the diagnosis could not be made by routine examination, VATS and even thoracotomy were undertaken. Serum and pleural total protein, albumin, total cholesterol, triglyceride, and HDL-cholesterol were measured by colorimetric method; serum and pleural LDH by enzymatic method; serum and pleural LDL-cholesterol by homogeneous LDL-cholesterol method; Apolipoprotein-A1, apolipoprotein-B, and lipoprotein-A by enhanced immunoturbidimetric method; and serum and pleural ADA levels by enzymatic kinetic method.

Statistical Package for the Social Sciences (SPSS 18.0 for Windows) was used for statistical analysis. Results on continuous measurements are presented as Mean ± 1SD. Mann-Whitney U test was used to compare the means of the groups. $P< 0.05$ value was accepted as statistical significance. Sensitivity, specificity, and positive and negative predictive index were calculated for each biochemical parameter. The Receiver operating characteristic curves (ROC) analysis was used to estimate the optimum cut-off value for the highest sensitivity and specificity.

Results

A total of 63 patients were evaluated for the study, of which 11 were excluded due to equivocal diagnosis. Thirty-five of the eligible 52 cases were exudate and the 17 others were transudate. The mean age of all cases was 62.8 ±17.0. Twenty-two of the exudate and 12 of the transudate group were male, and the mean ages of exudate and transudate groups were 59.8±17.6 and 68.9±14.0, respectively. The distribution of the etiologic factors is shown in Figure 1.

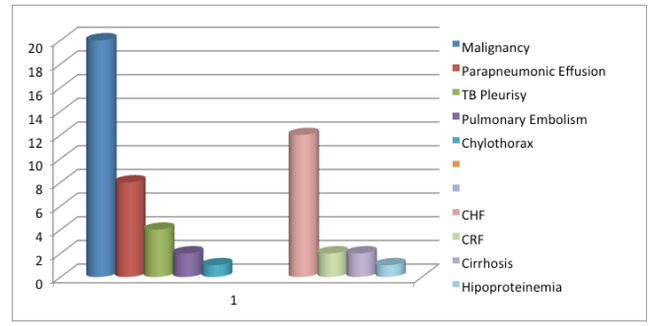

Figure1. The etiologic factors of the pleural effusions

The mean values of LDH, ADA, total protein, albumin, triglyceride, total cholesterol, HDL-cholesterol, VLDL-cholesterol, LDL-cholesterol, apolipoprotein A1, and HDL/LDL ratio in the pleural fluid were calculated and compared using the Mann-Whitney U test (Table 1).

Table 1. The comparison of biochemical parameters in the pleural fluid.

Parameter	Exudative	Transudative	P value
pLDH (IU/L)	835.9±651.8	216±112.4	0.001
pADA (IU/L)	6.9±8.1	5.6±5.5	0.423
pT. Protein (gr/dl)	3.8±1.1	2.5±1.3	0.001
pAlbumin (gr/dl)	2.2±0.8	1.3±0.7	0.001
pTriglyceride (mg/dl)	50.3±66.0	16.9±7.8	0.001
pT. Cholesterol (mg/dl)	68.8±33.1	31.7±19,2	0.001
pHDL-Cholesterol (mg/dl)	21.7±12.4	15.0±7,1	0.042
pVLDL-Cholesterol (mg/dl)	10.1±13.2	3.4±1.6	0.001
pLDL-Cholesterol (mg/dl)	38.4±26.8	15.4±15.1	0.001
pApolipoprotein A1 (mg/dl)	25.1±15.9	17.6±18.7	0.021
pHDL/LDL	4.0±3.9	5.0±2.5	0.048

The sensitivity, specificity, positive and negative predictive values of Light's criteria, pLDH, pTotal cholesterol, pHDL-cholesterol, pLDH+ pTotal cholesterol, and pLDH+ pTotal cholesterol+pHDL-cholesterol were calculated. The highest sensitivity and specificity were achieved when pLDH (232 IU/L), pTotal cholesterol (40.5 mg/dL), and pHDL-cholesterol (13.5 mg/dL) values were combined (Table 2).

Table 2. Sensitivity, specificity, positive predictive value, and negative predictive value of different biochemical parameters.

	Sensitivity	Specificity	PPV	NPV
Light (P/S LDH and P/S Albumin)	97%	65%	85%	91%
pLDH (232 IU/L)	94,3%	76,4%	89,2%	86,6%
pTotal cholesterol (40,5 mg/dL)	91%	82,3%	91%	82,3%
pHDL-cholesterol (13,5 mg/dL)	80%	64,7%	82.3%	61,1%
pLDH (232IU/L) + pTotal cholesterol (40,5 mg/dL)	97,2%	83%	92%	93%
pLDH (232IU/L) + pTotal cholesterol (40,5 mg/dL) + pHDL-cholesterol (13,5 mg/dL)	97,2%	94,12%	97,2%	94,12%

Receiver operating characteristics (ROC) curves of all parameters were drawn and area under the curves (AUC) of the highest 3 parameters, namely pLDH, pTotal cholesterol, and pHDL-

cholesterol, were calculated. The AUC of the pLDH, pTotal cholesterol, and pHDL-cholesterol were 0.899, 0.873, and 0.742 respectively (Figure 2).

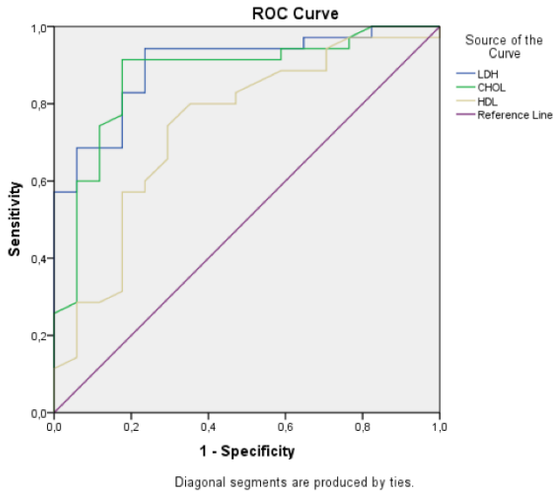

Figure 2. Receiver operating characteristic (ROC) curves for pleural LDH, cholesterol, and HDL-cholesterol concentrations as diagnostic tests for differentiating exudates from transudates.

Discussion

Though using Light's criteria was the most common method to differentiate exudative from transudative pleural effusions, previous reports in the literature were not able to confirm its results [4,5]. Besides, Light's criteria require both blood taking and thoracentesis from the patients. For this reason, researchers have long been looking for a new parameter both sufficiently sensitive and specific and also easy and cheap to perform. The current study showed 97% sensitivity and 65% specificity, and these figures were consistent with the literature [2,3,4,5,6]. Joseph et al. reported sensitivity and specificity of LDH level 377 IU/L or above in pleural fluid as 74% and 83% respectively [7]. Another study reported a higher sensitivity [93%] but a lower specificity (63%) when LDH levels were taken at 207 IU/L or above [8].

Cholesterol levels have long been investigated to differentiate exudates from transudates as an alternative to Light's criteria [9,10,11,12]. The exact mechanism of increased levels of cholesterol in pleural fluid is not known. It has been thought that degeneration of white or red blood cells could be the reason. Another hypothesis is that increased permeability might play a role [13,14]. Valdes et al. [9] were the earliest researchers investigating the role of pleural cholesterol levels in differentiating exudates from transudates, and reported very high sensitivity and specificity values. Gil Suay et al. [10] reported that when only the pleural cholesterol level of 54 mg/dL or above was taken into account, they found the sensitivity and specificity as 95% and 91%. Though they added serum cholesterol, and used the pleural cholesterol/serum cholesterol ratio of 0.32 as a reference value, the sensitivity and specificity did not change (97% and 91%). Another study that analyzed the value of pleural cholesterol levels in separation of exudates from transudates in 60 children, with a cut-off value of 40, found very high sensitivity, specificity, positive and negative predictive values [11].

In contrast to the many studies reporting high sensitivity and specificity values, Gasquez et al. [12] compared pleural cholesterol levels and Light's criteria in distinguishing exudates from transudates, and found that pleural cholesterol levels were less successful with relatively lower sensitivity and specificity values.

This study reported that when pLDH level 232 IU/L or above and pTotal cholesterol level 40.5 mg/dL or above were chosen, the sensitivity, specificity, PPV, and NPV were found as 97%, 83%, 92%, and 93%. When pHDL-cholesterol level 13.5 mg/dL was added to the pLDH and pTotal cholesterol, specificity and PPV rose to 97% and 94% respectively. Razi et al. studied 119 patients; when the pleural cholesterol level was chosen 38 mg/dL and above, they found the sensitivity and specificity as 87% and 79% respectively [15]. Recent studies from Hamal and Patel reported different pleural cholesterol cut-off levels but found similar sensitivity and specificity levels [16,17].

Kokturk et al. used pleural HDL-cholesterol/LDL-cholesterol ratio to differentiate exudates from transudates and reported that this ratio was significantly higher in transudates than in exudates [p=0.001]. When this ratio was chosen as 0.6, sensitivity and specificity were found as 89% and 79% respectively [18]. In the current study, a cut-off value for HDL-cholesterol/LDL-cholesterol could not be calculated but pleural HDL-cholesterol level alone was found useful for differentiating transudates from exudates [p=0.042]. Atalay et al. reported that pleural ADA level was more significant than albumin and protein gradient in differentiating exudates from transudates [19]. But this study did not find that ADA level was significant in differentiating between exudates and transudates.

In conclusion, although Light's criteria have been routinely used in differentiating exudates from transudates, it is clear that easier and cheaper methods are needed. Pleural cholesterol measurement is more accurate than Light's criteria. Combining pleural LDH, total cholesterol, and HDL-cholesterol measurements is very accurate and also very easy, and does not even require blood taking. But larger scale studies are needed to support these findings.

Abbreviations

p VLDL-cholesterol: Very low density lipoprotein level in pleural fluid

pHDL-cholesterol: High density lipoprotein level in pleural fluid

pLDH: Lactate dehydrogenase level in pleural fluid

p/s LDH ratio: Ratio of lactate dehydrogenase level in pleural fluid to lactate dehydrogenase level in serum

p/s Albumin ratio: Ratio of albumin level in pleural fluid to albumin level in serum

ROC: Receiver operating characteristic

PPV: Positive predictive value

NPV: Negative predictive value

Competing interests

The authors declare that they have no competing interests.

This study was approved in 2005 by the ethical committee of University of Bulent Ecevit, Zonguldak.

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